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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/663,875 | 09/16/2003 | Shi-Lung Lin | 89188.0050 | 3099 |

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| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |
| ART UNIT | PAPER NUMBER |
| 1635 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 07/22/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/663,875 | LIN ET AL. | |
| | Examiner | Art Unit | |
| | KIMBERLY CHONG | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,11,19 and 58-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,19,58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed 04/16/2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/16/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 04/16/2010, claims 1-8, 11, 19 and 58-60 are pending and currently under examination in the application.

### *New Rejections Necessitated by Claim Amendments*

### *Claim Rejections - 35 USC § 103*

Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al. (US Patent No. 7,393,632), Mitchell et al. (of record cited on form 892 mailed 03/11/2008), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54 of record PTO Form 892 mailed 03/11/2008), Zhuang et al. (PNAS Vol. 86: 2752-2756 of record PTO Form 892 mailed 03/11/2008, Coolidge et al. (of record cited on 892 mailed 01/23/2009) and Bennett et al. (US Patent No. 6,710,174)

The instant claims are drawn to an isolated RNA comprising an artificial intron RNA that is released in a cell thereby modulating the function of a target gene wherein the cell is a mammalian or a eukaryotic cell and wherein the target gene is integrin B1.

Cheo et al disclose a method for inducing RNA splicing-/processing-associated gene silencing effects in cultured eukaryotic cells, comprising synthesizing nucleic acid expression constructs comprising a plurality of desired nucleic acid molecules, wherein a first nucleic acid molecule may encode a protein of interest and wherein a second nucleic acid molecule may encode a gene-silencing RNA, e.g. a ribozyme or antisense molecule. Cheo et al disclose the nucleic acid sequence encoding a gene-silencing RNA may encode a sense, anti-sense or hairpin RNA (see at least figure 20D) and disclose that the gene-silencing artificial RNA may be present in a nucleic acid sequence comprising a recombination site that can be removed from the transcript using intron and exon splice sequences (see Examples 13 and 14).

Bennett et al. teach exon regions are preferred target sites for inhibitory nucleic acid molecules (see at least column 7).

Davey et al. teach antisense molecules targeted to a gene encoding an integrin beta 1 gene (see at least page 4664).

It would have been obvious to those of ordinary skill in the art to substitute the target gene taught by Cheo et al. with the integrin beta 1 gene taught by Davey et al. One would have been motivated because it was routine in the art to use any particular target gene to study the roles of said gene and given what was taught by Davey et al. regarding expression of integrin beta 1, the skilled artisan would have wanted to study

this genes function in cells. Moreover, it is well known in the art that exon regions are preferred target sites for inhibitory nucleic acid molecules such as antisense compounds as taught by Bennett et al. and it would have been obvious to target said region.

Thus absent evidence to the contrary, the invention as a whole would have been prima facie obvious.

### *Response to Arguments*

### *Claim Rejections - 35 USC § 112*

The rejection of claims 58-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

### *Claim Rejections - 35 USC § 102*

The rejection of claims 1, 2, 3, 7, and 11 under 35 U.S.C. 102(e) as being anticipated by Cheo et al. (US Patent No. 7,393,632) is maintained for the reasons of record.

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues Cheo et al. fails to disclose an isolated RNA comprising an artificial intron RNA that is released into a cell thereby silencing the function of a target gene.

This argument is not convincing. Cheo et al disclose a method for inducing RNA splicing-/processing-associated gene silencing effects in cultured eukaryotic cells, comprising synthesizing nucleic acid expression constructs comprising a plurality of desired nucleic acid molecules, wherein a first nucleic acid molecule may encode a

protein of interest and wherein a second nucleic acid molecule may encode a gene-silencing RNA, e.g. a ribozyme or antisense molecule. Cheo et al disclose the nucleic acid sequence encoding a gene-silencing RNA may encode a sense, anti-sense or hairpin RNA (see at least figure 20D) and disclose that the gene-silencing artificial RNA may be present in a nucleic acid sequence comprising a recombination site that can be removed from the transcript using intron and exon splice sequences (see Examples 13 and 14). Thus Cheo et al. teach a RNA comprising an RNA that can be spliced out of a nucleic acid wherein the RNA is capable of silencing a target gene and therefore anticipates the instant invention.

***Claim Rejections - 35 USC § 103***

The rejection of claims 1-8, 11, and19 under 35 U.S.C. 103(a) as being unpatentable over Cheo et al. (US Patent No. 7,393,632), Mitchell et al. (of record cited on form 892 mailed 03/11/2008), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54 of record PTO Form 892 mailed 03/11/2008), Zhuang et al. (PNAS Vol. 86: 2752-2756 of record PTO Form 892 mailed 03/11/2008, Coolidge et al. (of record cited on 892 mailed 01/23/2009) and Bennett et al. (US Patent No. 6,710,174) is maintained for the reasons of record.

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues Cheo et al. fails to disclose an isolated RNA comprising an artificial intron RNA that is released into a cell thereby silencing the function of a target gene.

Response to Cheo et al. is as above.

Applicant argues the references Mitchell, Krawczak, Zhuang, Coolide or Bennett do not remedy the defects in Cheo et al. and reiterates the teachings of each reference individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As stated previously, one of skill in the art would have been motivated to incorporate the acceptor site taught by Mitchell as it is shown this site efficiently allow proper splicing of therapeutic pre-mRNA sequence and one would have wanted to use the 5' donor splice site because Krawczak et al. teach the efficiency of splicing is critically dependent upon the accuracy of cleavage and rejoining and given this splice donor sequence has been identified as a consensus sequence for splicing, one would have wanted to use the most effective sequence to allow accurate splicing activity in cells to release the sequence as taught by Cheo et al. One of skill in the art would have been further motivated to use the branch site sequence taught by Zhuang et al. because Zhuang et al. demonstrated that this sequence is preferred in mammalian cells for accurate splicing of mRNA sequence. Given Coolidge et al. teach the sequence of the polypyrimidine tract is flexible but must contain at least a threshold of eight uridines, it would have been a matter of routine experimentation to the skilled artisan to construct and test polypyrmidine tracts that would contain the claimed sequence and incorporate

the optimal sequence into the claimed RNA. Moreover, it is well known in the art that exon regions are preferred target sites for inhibitory nucleic acid molecules such as antisense compounds as taught by Bennett et al. and it would have been obvious to target said region.Finally, one would have expected to be able to incorporate the sequences taught by Mitchell et al., Krawczak et al. and Zhuang et al. into the DNA template for the isolated RNA given both demonstrate that each sequence is capable of mRNA splicing and further teach said sequence is the preferred sequence for accurate splicing of mRNA in cells. One would have expected to be able to make and find the optimal polypyrimidine tract because Coolidge et al. teach how to make the optimal composition.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

## ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Christopher Low at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635